

# The Effect of Genetic Differences and Ovarian Failure: Intact Cognitive Function in Adult Women with Premature Ovarian Failure *Versus* Turner Syndrome

JUDITH L. ROSS, GERRY A. STEFANATOS, HARVEY KUSHNER, CAROLYN BONDY, LAWRENCE NELSON, ANDREW ZINN, AND DAVID ROELTGEN

*Department of Pediatrics (J.L.R.), Thomas Jefferson University, Philadelphia, Pennsylvania 19107; MossRehab Research Institute (G.A.S.), Albert Einstein Medical Center, Thomas Jefferson University, Philadelphia, Pennsylvania 19141; Biomedical Computer Research Institute (H.K.), Philadelphia, Pennsylvania 19115; Developmental Endocrinology Branch (C.B., L.N.), National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892; Eugene McDermott Center for Human Growth and Development and Department of Internal Medicine (A.Z.), The University of Texas Southwestern Medical School, Dallas Texas 75390; and Department of Medicine (Neurology) (D.R.), Pennsylvania State College of Medicine, Hershey, Pennsylvania 17033*

Premature ovarian failure (POF) is generally defined as amenorrhea, hypogonadism, and elevated gonadotropins occurring in a woman before the age of 40 yr. Usually, the etiology is unknown. Turner syndrome (TS, monosomy X), also associated with ovarian failure, has a characteristic neurocognitive profile. TS females, as a group, have specific deficits in visual-spatial abilities, visual-perceptual abilities, motor function, nonverbal memory, executive function, and attentional abilities. Observed deficits in TS could be due to endocrine (estrogen deficiency) or genetic factors. If early estrogen deficiency contributes to the cognitive deficits in TS, women with POF would also be at risk for similar findings.

The objective of this work was to examine the specific cognitive profile in women with POF and compare it with women with TS and normal female controls. We compared two unique populations (women with POF *vs.* TS), both with earlier estrogen deficiency. The TS group only had a major genetic deficiency, absence of all or part of one X chromosome.

We evaluated the cognitive performance of estrogen-repleted women with POF ( $n = 89$ ), compared with verbal IQ- and socioeconomic status-matched females with TS ( $n = 94$ ) and controls ( $n = 96$ ).

Performance by the POF population was similar to that of controls and differed from the TS population. In contrast, TS adults had relative difficulty with measures of spatial/perceptual skills, visual-motor integration, affect recognition, visual memory, attention, and executive function. These deficits are apparent in TS women, despite apparently adequate estrogen treatment.

The cognitive phenotypes of women with POF and normal controls are similar and differ from women with TS, indicating that prior estrogen deficiency does not have a major impact on cognitive function in adult females. The genetic deficiencies of women with TS most likely account for their specific cognitive phenotype. (*J Clin Endocrinol Metab* 89: 1817–1822, 2004)

**P**REMATURE OVARIAN FAILURE (POF) is generally defined as amenorrhea, hypogonadism, and elevated gonadotropins occurring in a woman before the age of 40 yr. Approximately one in 100 women develop POF before age 40, and an estimated one in 1000 women suffers POF before age 30 (1). POF has many genetic and nongenetic causes (2). In particular, disorders of the X chromosome, including partial or complete monosomy X [Turner syndrome (TS)] are associated with POF (3); however, most cases of POF without X chromosome abnormalities are idiopathic.

By definition, POF is associated with deficiency of estrogen for varying intervals in young women. Estrogen treatment is considered to be standard medical therapy in this

young adult population, in contrast to older, postmenopausal women. Populations of estrogen-deficient women previously studied include women with surgical ovariectomy, those with TS (monosomy X), and postmenopausal women. Previous estrogen treatment effects on cognition and behavior in a variety of estrogen-deficient populations have been reported as beneficial, in particular with verbal memory in some studies (4–13) and not others (14–16). A subset of neurocognitive deficits in TS (memory, reaction time, and speeded motor function) may result from estrogen deficiency. These particular deficits are, at least partially, reversed with estrogen treatment therapy in early adolescence (17, 18). Surgically induced menopause is associated with immediate decrements in estrogen as well as changes in cognition, specifically involving verbal memory (19). Thus, if previous estrogen deficiency gives rise to alterations in cognitive function, as occurs in TS, these differences would also be observed in women with POF.

The goal of this particular study was to comprehensively evaluate cognitive function in two groups of women with ovarian failure: women with POF (normal karyotype); and women with monosomy X, TS. Both groups received stan-

Abbreviations: ANCOVA, Analysis of covariance; ERT, estrogen replacement therapy; IQ, intelligence quotient; PANES, Physical and Neurological Examination of Soft Signs; POF, premature ovarian failure; SES, socioeconomic status; TS, Turner syndrome; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised; WRAT-III, Wide Range Achievement Test-III.

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dard estrogen replacement therapy (ERT). POF represents an important group to study, particularly in comparison with TS women who have a well-defined neurocognitive phenotype (20). Both groups experience estrogen deficiency and undergo replacement therapy. We predicted that women with POF would have normal cognitive function, compared with control females, and would differ from women with TS.

## Subjects and Methods

This study was approved by the Human Studies Committees at Thomas Jefferson University and the National Institute of Child Health and Human Development at the NIH. Informed consent was obtained in all cases.

### Participants

**Women with POF.** Women with POF ( $n = 96$ ), ages 18–49 yr, participated in the study; 90% were right-handed, and 89% were Caucasian. Participants were recruited through Thomas Jefferson University Hospital and the NIH. All participants had normal karyotypes. Spontaneous POF was diagnosed before age 40 and was defined by at least 4 months of amenorrhea, two FSH levels above 40 mIU/ml, at least 1 month apart, and a normal 46,XX karyotype. Additionally, all were receiving ERT (estrogen and progesterone sequentially, 100- $\mu$ g estradiol patch, and 12 d of medroxyprogesterone per month, or oral contraceptives or others) at the time of the evaluation. All had apparently normal menstrual cycles and adult breast development at the time of the evaluation. Because estrogen treatment is the standard of care, a comparison group of non-estrogen-treated women with POF could not be included. The age of onset of ovarian failure and the number of years of ERT were calculated for each study participant.

**Control women.** Normal female controls ( $n = 96$ ), ages 18–49 yr, were recruited from Philadelphia and Maryland. They were all healthy, non-pregnant, regularly menstruating women (cycles between 21 and 35 d). Within the controls, 89% were right-handed, and 75% were Caucasian. All were between the 5th and 95th percentiles for height and weight and had no significant past medical history.

**TS.** Adult women with TS ( $n = 94$ ) were included. Within the TS population, 86% were right-handed, and 91% were Caucasian. They qualified for the study if they met the following criteria: karyotype diagnosis compatible with TS: 1) 45,X; 2) mosaic for 45,X and a second cell line (46,XX, isochromosome X, or 47,XXX); or 3) partial deletion of the 2nd X chromosome including nonmosaic isochromosome X. Participants containing any Y chromosome material in the peripheral karyotype were excluded from the study. All were receiving ERT (e.g. estrogen and progesterone sequentially, oral contraceptives). A subset of the TS patients ( $n = 36$ ) discontinued estrogen 2 wk before the evaluation. No TS women were receiving unusual medications or experiencing symptoms of an underlying medical or psychiatric or abusing substances that would alter cognitive test performance.

The age of onset of ovarian failure and the number of years of ERT were calculated for each study participant. Results from a subset of these patients were previously reported (20).

### Design and procedure

Participants were administered a battery of cognitive tests designed to assess the following broad domains of cognitive function: general intellectual ability, academic achievement, verbal and nonverbal memory, language, executive function, visual/spatial-perceptual skills, visual-motor skills, motor skills, attention/impulsivity, and affect discrimination. Socioeconomic status (SES) levels were derived according to the method of Hollingshead and Redlich (21) based on education and occupation of parents. All testing was conducted at Thomas Jefferson University Hospital or the NIH by trained psychometricians. The neuropsychologist (G. A. Stefanatos) was closely affiliated with this study.

### Data analysis

Descriptive statistics were used to provide demographic information of participants, including age and SES. In addition, performance means and sds for each task are provided. Analysis of covariance (ANCOVA) was performed, examining the effect of group, age, and SES on the POF, TS, and control groups. Pairwise, *post hoc* tests were performed when significant group differences occurred on ANCOVA. Last, Pearson correlations were performed for the POF group only, looking at effects of age of diagnosis of POF and previous duration of estrogen treatment.

Effect sizes (equal difference in means divided by pooled sds) are indicated in the tables. Unadjusted *P*-values are provided, and the level of significance needed when using a Bonferroni adjustment is also provided. The Bonferroni adjustment is based on the number of tests within each domain.

### Power analysis

With POF and control sample sizes of 89 and 96, respectively, we had an 80% power to detect a moderate effect size of 0.41.

## Results

The POF, TS, and control groups were well-matched for age (Table 1). SES was slightly decreased in the TS group *vs.* the POF and control groups ( $P < 0.01$ ).

### General cognition results

Evaluation of intellectual abilities did not demonstrate any significant differences among the POF, TS, and control women on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) verbal IQ (intelligence quotient) score. Analysis of individual subtests on the WAIS-R also revealed that performance of POF women and controls was similar. The POF group had mildly diminished performance on digits backward but not digits forward (Table 2). The ANCOVA did not reveal any age effects on any of the cognitive variables within the table. Within the POF group, there were no significant effects of age at diagnosis or duration of estrogen treatment on any of the variables in Table 2 (data not shown). The TS population had depressed scores on digit span and multiple performance IQ subtests, compared with both the normal control and POF groups. In addition, they had lower scores on the arithmetic subtest. Analogous findings were not observed in the POF population.

### Verbal and nonverbal memory abilities

Table 3 includes results of measures of verbal memory [logical stories subtest of the Wechsler Memory Scale-Revised (WMS-R), Word list] and nonverbal memory (Rey-Osterrieth Complex Figure test—immediate and delayed recall, WMS-R visual memory, and Warrington Faces). POF females performed at levels comparable with those of controls on measures of both verbal and nonverbal memory. Although the POF women performed slightly less well than controls on two measures of immediate verbal memory (trial 1 recall on the word list and WMS-R immediate but not

**TABLE 1.** Demographic information

	POF	Control	TS
<b>n</b>	89	96	94
Chronologic age (yr)	34.5 $\pm$ 6.6	33.5 $\pm$ 7.7	31.2 $\pm$ 9.7
SES	53 $\pm$ 11	53 $\pm$ 10	49 $\pm$ 11

**TABLE 2.** General cognitive and verbal abilities (mean  $\pm$  SD, ANCOVA)

WAIS-R (29)	POF	Control	TS	<i>P</i> <sup>a</sup>			Effect size	
				Group	Age	SES	POF <i>vs.</i> TS	TS <i>vs.</i> control
n	89	96	94					
Verbal IQ	104 $\pm$ 12	107 $\pm$ 13	102 $\pm$ 11	0.09	0.91	0.001	0.17	0.42
Performance IQ	107 $\pm$ 13	108 $\pm$ 14	94 $\pm$ 10	0.001 <sup>b,c</sup>	0.71	0.001	1.13	1.17
Full-scale IQ	106 $\pm$ 12	108 $\pm$ 12	98 $\pm$ 10	0.001 <sup>b,c</sup>	0.68	0.001	0.73	0.91
Subtest information	11.0 $\pm$ 2.2	11.4 $\pm$ 2.6	11.5 $\pm$ 2.3	0.14	0.57	0.001	0.22	0.04
Similarities	10.6 $\pm$ 2.5	11.2 $\pm$ 2.5	10.8 $\pm$ 2.6	0.17	0.13	0.002	0.08	0.16
Arithmetic	10.6 $\pm$ 2.5	11.0 $\pm$ 2.5	9.4 $\pm$ 2.6	0.002 <sup>b,c</sup>	0.70	0.001	0.47	0.63
Vocabulary	11.5 $\pm$ 2.8	11.6 $\pm$ 2.7	11.3 $\pm$ 2.6	0.99	0.76	0.001	0.07	0.11
Comprehension	10.1 $\pm$ 2.2	10.7 $\pm$ 2.6	9.8 $\pm$ 2.1	0.14	0.50	0.001	0.14	0.38
Digit span (DS)	10.2 $\pm$ 2.5	10.9 $\pm$ 2.9	9.1 $\pm$ 2.4	0.001 <sup>b,c</sup>	0.84	0.03	0.45	0.68
DS forward <sup>d</sup>	8.4 $\pm$ 2.2	8.7 $\pm$ 2.2	7.6 $\pm$ 2.0	0.007 <sup>b</sup>	0.71	0.002	0.38	0.52
DS backward <sup>d</sup>	6.9 $\pm$ 1.9	7.7 $\pm$ 2.6	6.1 $\pm$ 2.2	0.001 <sup>b</sup>	0.49	0.18	0.39	0.7
Picture completion	11.5 $\pm$ 2.6	11.3 $\pm$ 2.7	9.0 $\pm$ 2.3	0.001 <sup>b,c</sup>	0.55	0.03	1.02	0.92
Picture arrangement	10.2 $\pm$ 2.3	10.7 $\pm$ 2.5	9.2 $\pm$ 2.5	0.001 <sup>b</sup>	0.73	0.07	0.42	0.60
Block design	11.0 $\pm$ 2.7	11.6 $\pm$ 2.6	9.3 $\pm$ 2.7	0.001 <sup>b,c</sup>	0.52	0.001	0.63	0.87
Object assembly	10.6 $\pm$ 3.1	10.2 $\pm$ 2.9	8.8 $\pm$ 2.6	0.001 <sup>b,c</sup>	0.21	0.03	0.63	0.51
Coding/dig symbol	11.3 $\pm$ 2.5	12.1 $\pm$ 2.7	9.7 $\pm$ 2.5	0.001 <sup>b,c</sup>	0.29	0.02	0.64	0.92

<sup>a</sup> ANCOVA examining group for main effect and age and SES as covariates; after a Bonferroni adjustment,  $P < 0.001$  would be statistically significant.

<sup>b</sup> Post hoc tests  $P$ -value ( $<0.001$ ): <sup>b</sup> TS *vs.* controls; <sup>c</sup> TS *vs.* POF.

<sup>d</sup> Longest digit string performed correctly.

**TABLE 3.** Memory: verbal and nonverbal (mean  $\pm$  SD)

Verbal memory	POF	Control	TS	<i>P</i> <sup>a</sup>			Effect size	
				Group	Age	SES	POF <i>vs.</i> TS	TS <i>vs.</i> control
n	89	96	94					
WMS-R (30) immediate recall	27 $\pm$ 8	29 $\pm$ 6	29 $\pm$ 7	0.09	0.05	0.001	0.27	0.01
Delayed recall	24 $\pm$ 8	25 $\pm$ 7	23 $\pm$ 8	0.29	0.08	0.001	0.13	0.27
Word list (31) immediate recall (trial-I)	7.0 $\pm$ 2.0	7.8 $\pm$ 1.9	6.3 $\pm$ 2.4	0.001	0.02	0.01	0.32	0.70
Nonverbal memory								
Rey-immediate recall (32, 33)	37 $\pm$ 11	39 $\pm$ 12	29 $\pm$ 14	0.001 <sup>b,c</sup>	0.001	0.28	0.64	0.77
Rey-delayed recall	36 $\pm$ 10	36 $\pm$ 12	25 $\pm$ 13	0.001 <sup>b,c</sup>	0.001	0.67	0.96	0.88
WMS-R visual memory (30)	16.3 $\pm$ 2.7	16.8 $\pm$ 3.1	14 $\pm$ 3	0.001 <sup>b,c</sup>	0.001	0.007	0.81	0.92
Warrington faces (34)	43 $\pm$ 4	43 $\pm$ 5	40 $\pm$ 4	0.001 <sup>b,c</sup>	0.34	0.03	0.75	0.67

<sup>a</sup> ANCOVA examining group for main effect and age and SES as covariates; after a Bonferroni adjustment,  $P < 0.002$  would be statistically significant.

<sup>b</sup> Post hoc tests  $P$ -value ( $<0.001$ ): <sup>b</sup> TS *vs.* controls; <sup>c</sup> TS *vs.* POF.

delayed recall), the differences in the group means were not statistically significant. ANCOVA revealed significant age effects for performance on several aspects of nonverbal memory, including Rey recall and the WMS-R visual memory span. Within the POF group, there were no significant effects of age at diagnosis or duration of estrogen treatment on any of the variables in Table 3. There were significant deficiencies in the TS group in nonverbal memory performance that were not present in the women with POF or in the controls.

#### Nonverbal abilities

Table 4 includes measures of nonverbal ability, including spatial perceptual tests (Gestalt Closure and Facial Recognition), visual-motor tests (Rey Figure-copy and Pursuit Rotor), math achievement (WRAT-III mathematics), and the Affect Recognition test. Analysis of nonverbal abilities demonstrated similar performance in the POF and control populations on tests of visual-perceptual skills, spatial abilities, visual-motor coordination, and affect recognition (Table 4).

On examination of visual affect recognition (Table 4), POF

females had somewhat greater difficulty discriminating one affective expression: fear. Significant age effects occurred for performance of the Pursuit Rotor and Gestalt Closure. There were no effects in the POF group of age of diagnosis or estrogen treatment duration.

The TS comparison group had impaired spatial perceptual performance on multiple tasks. They also had impaired affect recognition for several affects, including: anger.

#### Executive abilities

Table 5 includes measures of attention and executive function (Rey Figure-organization, verbal fluencies, and Word list cluster). POF females had normal performance on several tests of executive function. No age effects were noted on these tasks. Within the POF group, there were no significant effects of age at diagnosis or duration of estrogen treatment on any of the variables. In contrast, TS females performed significantly less well than POF females or controls on Rey organization and word fluencies but not on Word list cluster.

**TABLE 4.** Nonverbal abilities (spatial/perceptual, visual-motor, arithmetic, affect recognition) (mean  $\pm$  SD)

	POF	Control	TS	<i>P<sup>a</sup></i>			Effect size	
				Group	Age	SES	POF <i>vs.</i> TS	TS <i>vs.</i> control
n	89	96	94					
Spatial/perceptual								
Gestalt closure (35)	75 $\pm$ 13	76 $\pm$ 17	69 $\pm$ 16	0.002	0.001	0.28	0.41	0.42
Facial recognition (36)	47 $\pm$ 4	48 $\pm$ 3	43 $\pm$ 4	0.001 <sup>b</sup>	0.34	0.41	1.00	1.43
Visual-motor								
Rey-copy (32, 33)	65 $\pm$ 4	66 $\pm$ 5	60 $\pm$ 6	0.001 <sup>b,c</sup>	0.66	0.06	1.00	1.09
Pursuit rotor (37)	2.5 $\pm$ 1.5	2.1 $\pm$ 1.2	3.2 $\pm$ 1.5	0.001 <sup>b</sup>	0.001	0.04	0.47	0.81
Dominant hand-time off target								
Distance	147 $\pm$ 89	173 $\pm$ 88	106 $\pm$ 72	0.001 <sup>b,c</sup>	0.001	0.05	0.51	0.84
Pursuit rotor nondominant hand-time off target	3.4 $\pm$ 1.6	3.4 $\pm$ 1.6	4.5 $\pm$ 1.7	0.001 <sup>b,c</sup>	0.001	0.004	0.67	0.7
Distance	98 $\pm$ 73	97 $\pm$ 60	57 $\pm$ 40	0.001 <sup>b,c</sup>	0.02	0.07	0.73	0.80
Arithmetic achievement								
WRAT-R arithmetic (38)	99 $\pm$ 13	103 $\pm$ 14	95 $\pm$ 11	0.002 <sup>b</sup>	0.29	0.001	0.33	0.4
Standard score								
Affect recognition (43) % correct								
Happy	96 $\pm$ 9	97 $\pm$ 4	95 $\pm$ 6	0.06	0.44	0.03	0.13	0.40
Sad	73 $\pm$ 20	74 $\pm$ 19	66 $\pm$ 20	0.06	0.60	0.07	0.35	0.41
Fear	52 $\pm$ 25	64 $\pm$ 25	53 $\pm$ 26	0.02	0.69	0.49	0.04	0.43
Anger	84 $\pm$ 13	88 $\pm$ 14	78 $\pm$ 19	0.005 <sup>b</sup>	0.03	0.68	0.38	0.1
Surprise	96 $\pm$ 6	94 $\pm$ 8	92 $\pm$ 10	0.02	0.54	0.34	0.50	0.22
Disgust	85 $\pm$ 19	88 $\pm$ 17	86 $\pm$ 16	0.36	0.21	0.004	0.06	0.12
Time (sec)	333 $\pm$ 221	311 $\pm$ 82	369 $\pm$ 137	0.06	0.003	0.03	0.20	0.53

<sup>a</sup> ANCOVA examining group for main effect and age and SES as covariates; after a Bonferroni adjustment,  $P < 0.001$  would be statistically significant.

*Post hoc* tests  $P$ -value ( $<0.001$ ): <sup>b</sup> TS *vs.* controls; <sup>c</sup> TS *vs.* POF.

**TABLE 5.** Attention and executive function (mean  $\pm$  SD)

Test	POF	Control	TS	<i>P<sup>a</sup></i>			Effect size	
				Group	Age	SES	POF <i>vs.</i> TS	TS <i>vs.</i> control
n	89	96	94					
Rey figure organization (32)	11.1 $\pm$ 2.6	11.4 $\pm$ 2.4	9.0 $\pm$ 3.4	0.001 <sup>b,c</sup>	0.61	0.56	0.70	0.8
COWAT <sup>d</sup> (39)	43 $\pm$ 12	43 $\pm$ 10	34 $\pm$ 10	0.001 <sup>b,c</sup>	0.02	0.002	0.82	0.9
Semantic fluency <sup>e</sup> (39)	76 $\pm$ 17	74 $\pm$ 13	65 $\pm$ 14	0.001 <sup>b,c</sup>	0.02	0.03	0.71	0.6
Word list-cluster	3.3 $\pm$ 2.9	4.6 $\pm$ 3.8	3.6 $\pm$ 3.5	0.09	0.14	0.35	0.09	0.2

<sup>a</sup> ANCOVA examining group for main effect and age and SES as covariates; after a Bonferroni adjustment,  $P < 0.001$  would be statistically significant.

*Post hoc* tests  $P$ -value ( $<0.001$ ): <sup>b</sup> TS *vs.* controls; <sup>c</sup> TS *vs.* POF.

<sup>d</sup> COWAT performance is verbal fluency, based upon the total number of words generated for each of three letters (F, A, and S).

<sup>e</sup> Total number of categorical items generated for each of four semantic categories.

### Motor function

Table 6 includes measures of motor ability [pegboard and physical and neurological examination of soft signs (PANES)]. POF females and controls were analyzed on measures of simple motor skills (finger tapping test and tapping of the foot and of the index finger to thumb on the PANES) and more complex motor skills involving a spatial component (Lafayette pegboard). POF females performed at levels comparable with those of controls on both the simple motor tasks of the PANES (finger and foot tapping) and the more spatially dependent measure of motor skills (Lafayette pegboard, Table 6). No age effects were noted on performance. Within the POF group, there were no significant effects of age at diagnosis or duration of estrogen treatment on any of the variables in Table 6.

In contrast, performance by the TS females was much slower for the pegboard as well as PANES foot and finger tapping. The time required for performance of the alternating 4-finger PANES was similar in the three groups.

### Discussion

In this study, we contrasted two groups of women with ovarian failure and previous estrogen deficiency: women with POF, and women with TS. A normal female control group was also included. The three groups were matched for age and verbal IQ. On comprehensive neuropsychological assessment, the performance of POF women was similar to that of controls. This absence of differences was not related to small sample size (see power analysis). In contrast, the TS population had relatively impaired performance on measures of motor speed, nonverbal memory, spatial and visual-constructional abilities, and executive function. These findings are consistent with numerous previous reports (20, 22, 23).

The absence of cognitive differences between the POF women and controls suggests that estrogen supplementation is quite successful in preventing cognitive effects that may otherwise emerge in the context of estrogen deficiency. Some estrogen actions are genomic, mediated by intracellular



**TABLE 6.** Motor abilities (mean  $\pm$  SD)

Test	POF	Control	TS	<i>P</i> <sup>a</sup>			Effect size	
				Group	Age	SES	POF <i>vs.</i> TS	TS <i>vs.</i> control
n	89	96	94					
Pegboard-dom <sup>b</sup> (40)	48 $\pm$ 7	47 $\pm$ 7	55 $\pm$ 11	0.001	0.40	0.75	0.78	0.89
Pegboard-nondom	51 $\pm$ 9	50 $\pm$ 7	58 $\pm$ 11	0.001	0.13	0.55	0.70	0.89
PANES								
Foot tap-dom (41)	5.4 $\pm$ 1.0	5.8 $\pm$ 1.4	6.5 $\pm$ 1.6	0.001	0.07	0.11	0.85	0.47
Foot tap-nondom	5.6 $\pm$ 1.2	5.9 $\pm$ 1.8	6.4 $\pm$ 1.5	0.004	0.10	0.16	0.59	0.30
Finger tap-dom	4.1 $\pm$ 1.0	4.4 $\pm$ 1.3	4.6 $\pm$ 1.3	0.06	0.82	0.54	0.43	0.15
Finger tap-nondom	4.3 $\pm$ 1.0	4.7 $\pm$ 1.3	4.8 $\pm$ 1.4	0.02	0.93	0.69	0.42	0.07
Alternation-dom	25 $\pm$ 7	25 $\pm$ 5	26 $\pm$ 6	0.26	0.06	0.02	0.15	0.18
Alternation-nondom	26 $\pm$ 6	26 $\pm$ 6	27 $\pm$ 7	0.22	0.02	0.03	0.15	0.15

*Post hoc* tests *P*-value (<0.001) PANES measures: 1) foot tap is the time in seconds required to tap the foot 20 times; 2) finger tap is the time (seconds) required to tap the thumb and index finger together 20 times; 3) alternation is the time (seconds) required to tap thumb to each of the fingers in sequence 20 times.

<sup>a</sup> ANCOVA examining group for main effect and age and SES as covariates; after a Bonferroni adjustment, *P* < 0.002 would be statistically significant.

<sup>b</sup> dom, Dominant hand/foot as determined by the Crovitz method (42); nondom, nondominant hand/foot.

estrogen-induced changes in gene expression, whereas others are activational related to estrogen influences on signal transduction. Estrogen may also interact with neurotrophins, in concert and reciprocally, to stimulate synthesis of proteins required for neural differentiation, survival, and functional maintenance (24). The rate of alteration in estrogen levels may influence outcome. For example, surgically induced menopause results in immediate decrements in estrogen that are associated with equally precipitous changes in cognition, particularly involving verbal and visual memory (19). Exogenous ERT appears to exert influences on estrogen-sensitive neural processes comparable with those of endogenous estrogen, because there are no clinically significant differences in estrogen-supplemented women with POF, compared with normal controls.

Benefits have also been observed in postmenopausal women given ERT, but subtle differences may be missed against the background of age-related changes in cognitive function. Consequently, the beneficial cognitive effects of estrogen in the aging female population have been variable, with some studies reporting benefits (6, 9, 13) and others reporting no benefit (14–16). Moreover, the decline in estrogen in the postmenopausal population may occur at a time when its biological significance is decreasing and ERT is considered medically optional, or even contraindicated. By contrast, previous studies have shown beneficial, estrogen-related effects on cognition and behavior in a variety of younger estrogen-deficient populations, (4–13). These inconsistencies in the effect of ERT on cognition raise the possibility of an age-related gradient in the cognitive impact of ERT.

Both POF women and TS women produce decreased endogenous ovarian estrogen. Thus, if previous estrogen deficiency alone gives rise to long-term subsequent alterations in cognitive function, as occurs in TS, these differences would also be observed in the women with POF. Clearly, this is not supported by the present findings. The TS women may have more profound (earlier) ovarian failure than the women with POF who were more likely to have had some ovarian function through adolescence. As a result, estrogen levels in childhood and adolescence may have been somewhat lower in the TS women.

By definition, only the TS females in this study all had a genetic deficiency involving all or part of one X chromosome, whereas the POF women had normal chromosome karyotypes. There has been longstanding controversy regarding the degree to which the cognitive deficits that characterize TS are due to genetic deficiencies (missing gene/genes on the X chromosome, hormonal deficiencies, or some combination). The view that the neurocognitive deficits seen in TS could result from early deficiency of sex steroids is derived from the findings that a subset of these deficits (memory, reaction time, and speeded motor function) are at least partially reversed with ERT (17, 18). However, although replacement therapy exerts selected positive changes in neurocognitive function, its effects are subtle and only partially correct deficits in those domains. In contrast, other areas of cognitive function (visual-spatial/perceptual skills) are relatively consistent across wide age ranges in TS and are apparently not reversible with estrogen treatment.

There is converging functional and structural neuroimaging evidence that TS-associated limitations in certain cognitive domains are secondary to perturbations of neural development involving specific cortical areas. TS females have significantly smaller structures in several subcortical areas, including cerebellum and pons, thalamus and nuclei in both limbic (hippocampus), and striatal systems (caudate, lenticular nuclei) (25). Reductions have also been observed in cortical neuroanatomy, particularly in parieto-occipital areas bilaterally and the white matter tracts that connect these areas (genu of the corpus callosum), and the right temporal lobe (26). The extent of some of these structural differences appears related, at least in part, to the degree of monosomy X; TS cases with a mosaic karyotype had relatively fewer anomalies than the those with the nonmosaic, 45,X karyotype (27).

These findings point to anomalies in cortical organization that may account for the characteristic spectrum of TS neuropsychological deficits. Based on current models of neurocognitive function, it is possible to speculate that the involvement of subcortical structures may contribute to their problems with attention and motor coordination, whereas the bilateral involvement of posterior cortex (temporal, parietal) may relate more to their visual-perceptual and spatial information processing disturbances. Difficulties with facial

affect recognition may reflect a combination of anomalies in cortical and subcortical circuits (28). The functional implications of these structural findings is also supported by observations of reduction or asymmetries in cortical metabolism (26, 27).

In summary, our findings suggest that estrogen treatment in POF women results in essentially normal cognitive function, in contrast to TS women, in whom estrogen treatment does not result in normal cognitive function. These findings indicate that the persisting cognitive deficits in TS predominantly reflect fixed genetic deficiencies. ERT is clinically indicated and recommended as standard treatment in young women with POF; however, the duration of ERT remains an open question. Future studies are also needed to focus on gene/genes on the X chromosome that contribute to the early and persistent cognitive phenotype in women with TS.

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Address all correspondence and requests for reprints to: Judith L. Ross, M.D., Thomas Jefferson University, Department of Pediatrics, 1025 Walnut Street, Philadelphia, Pennsylvania 19107. E-mail: judith.ross@mail.tju.edu.

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